SYNTHESIS AND SPECTRAL STUDIES OF 4-FUNCTIONAL PYRAZOLYLTHIAZOLES AND THEIR BIOLOGICAL INVESTIGATION

SYNOPSIS

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SYNOPSIS

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1. **Title:** SYNTHESIS AND SPECTRAL STUDIES OF 4-FUNCTIONAL PYRAZOLYLTHIAZOLES AND THEIR BIOLOGICAL INVESTIGATION

2. Introduction

Pyrazoles are unique in their chemical behavior among heterocyclic compounds as well as related azoles (Alam et al 2015). Pyrazole is the core structure in a number of drugs such as difenamizole, tepoxalin (Abdel-Satter et al 2012), celecoxib, phenylbutazone (Gore 2015), zaleplon and indiplon (Hassan et al 2014). Due to the broad spectrum of applications in the field of medicines such as anti-inflammatory (Pandya et al 2012), bactericidal (Bozdaq-Dundar et al 2008), antitumor (Ahmed et al 2009), antiviral (El-Sabbagh et al 2009), anti-tubercular (Castagnolo et al 2009) and antioxidant properties (Magesh et al 2006), the researchers have a keen interest in pyrazole chemistry. Besides these properties, pyrazole derivatives with a phenyl group at 5 position also showed good film forming properties and exhibit excellent characteristics of blue photo luminescence and electro luminescence (Faritha et al 2014).

On the other hand, thiazole nuclei are ubiquitous motifs representing an interesting array of heterocyclic compounds exhibiting a wide range of biological activities such as antimicrobial, anti-inflammatory, anti-tubercular, anticonvulsant, anti-tumour, antibacterial and anticancer properties (Khloya et al 2015 and Karale et al 2015). Small and simple thiazole as well as benzothiazole nuclei have made their presence in drug arena as thiazole ring present in established carbonic anhydrase inhibitors (CAI) drugs like ethoxzolamide (EZA) (Sitaram et al 2014).

Pyrazole derivative incorporated with thiazole ring also showed a wide range of medicinal and pharmaceutical applications. They have potent antiviral, anti-inflammatory and antimicrobial activities (Dawood et al 2015).

To see the unique chemical behavior and interesting biological applications of pyrazole and thiazole derivatives and the idea that the incorporation of both pyrazole and thiazole together in the same scaffold could provide novel compounds with remarkable biological efficiency, we thought worthwhile to work on 4-functional pyrazolylthiazole derivatives.

The main objectives of the present research work are depicted below:

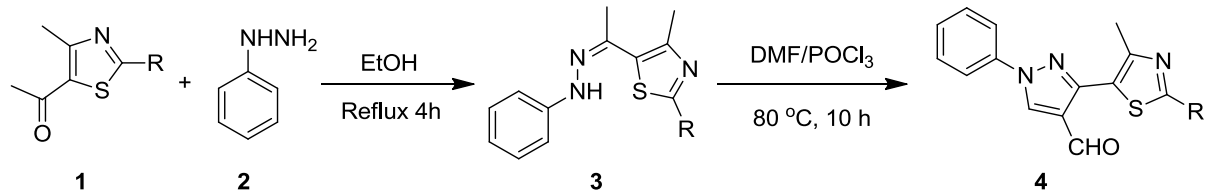
a) Development of synthetic routes and purification methods for the newly synthesized compounds.
b) Synthesis of 4-functionally substituted 1-thiazolylpyrazoles which are precursors for many nitrogen & sulphur containing heterocyclic compounds.
c) Characterization of new compounds by IR, ^{1}H NMR, Mass spectral studies and also by elemental analysis.
d) Evaluation of biological activities of new compounds, such as antimicrobial activity using different bacterial and fungal stains.

3. Expected new knowledge

Research studies have indicated the remarkable pharmacological efficiency of pyrazole and thiazole derivatives. The greatest impact of the dealing of heterocyclic chemistry is the development of new pharmaceutically active and efficient compounds. This gives us an opportunity to explore new molecules. Therefore, our studies are focused towards the synthesis of 4-functionally substituted 1-thiazolylpyrazoles by hybrid approach and used them for the biological evaluation. It is expected that the study of structure-activity relationship (SAR) of the new compounds will impart structural elements for new drug designing and synthesis of these compounds will impart a great role to extend the method to a broad range of different starting materials to find the scope and limitations.

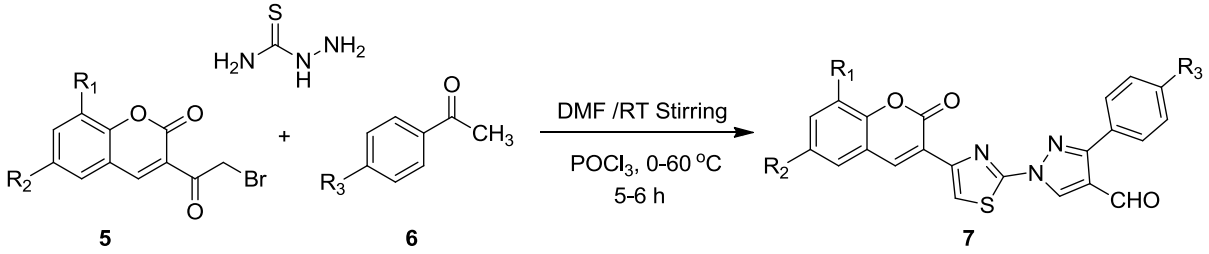
4. Review of literature

Khillare et al (2015) reported the synthesis and spectral study of 3-(4-methyl-2-substituted thiazol-5-yl)-1-phenyl-1H-pyrazol-4-carbaldehydes **4**. These target compounds **4** were prepared by Vilsmeier-Haack reaction on the hydrazones **3** at 80-90 ^{o}C using DMF/$POCl_3$ as formylating reagent. Hydrazones **3** were synthesized by condensing phenyl hydrazine and 5-acetyl thiazoles **1** using ethanol as a solvent.



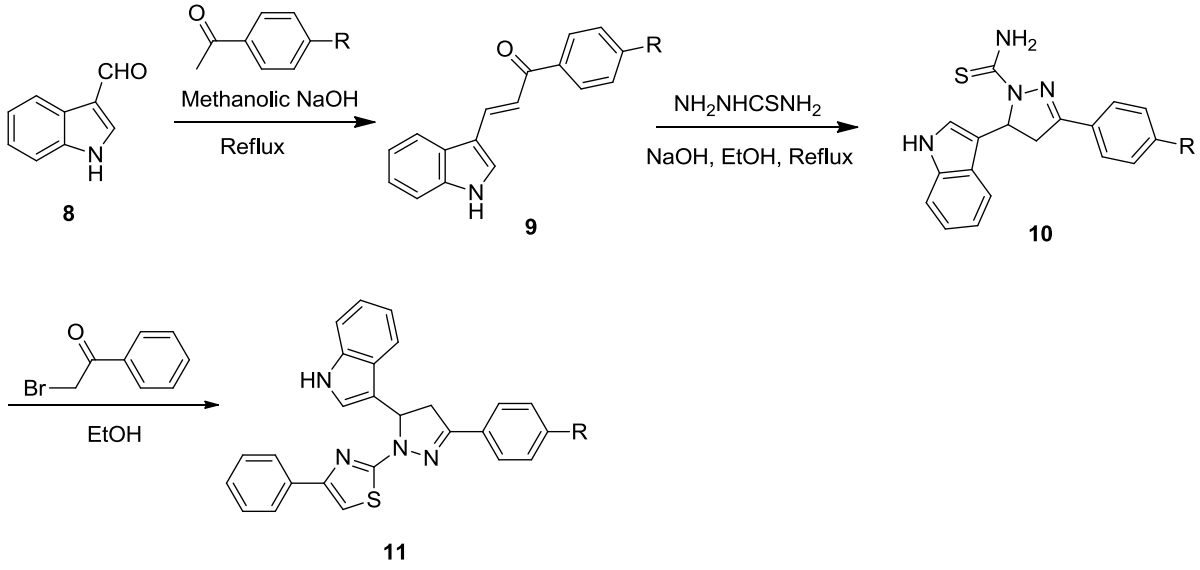
Scheme 1

Vaarla and co-workers (2015) reported an efficient, one-pot multi-component approach for the synthesis of coumarin substituted thiazolyl-3-arylpyrazole-4-carbaldehydes **7**. Treatment of 3-(2-bromoacetyl)coumarins **5**, thiosemicarbazide and substituted acetophenones **6** with Vilsmeier-Haack reagent resulted the target compounds **7** with good yields.



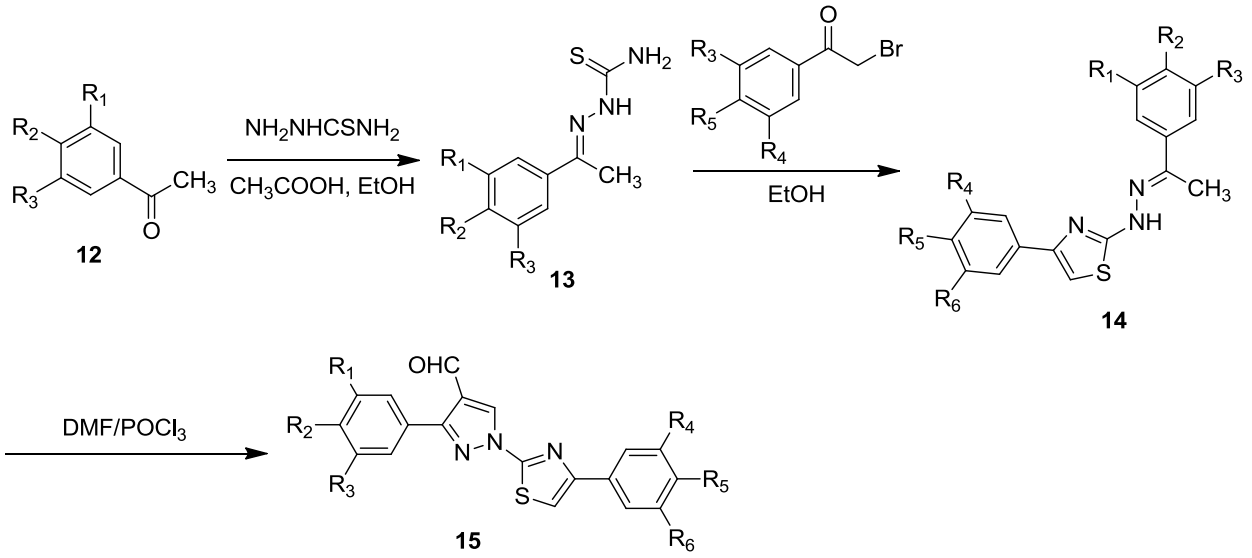
Scheme 2

Faritha et al (2014) reported the synthesis of 1-(4-phenyl thiazole-2-yl)-5-(1*H*-indol-3-yl)-3-substituted phenyl-4,5-dihydropyrazoles **11**. The chalcones **9** were synthesized via Claisen-Schmidt condensation between substituted acetophenone and 1H-indole-3-carbaldehyde (**8**). These chalcones were further treated with thiosemicarbazide to obtain thiosemicarbamoyl pyrazolines **10** which on condensation with phenacyl bromide furnish the target compound **11**.



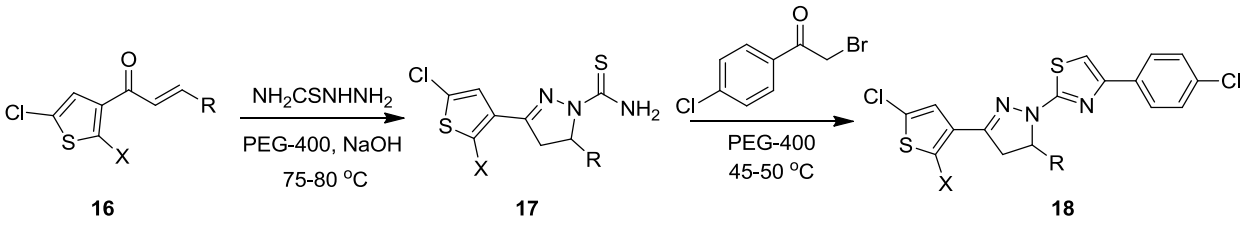
Scheme 3

Gaikwad et al (2013) reported the synthesis of 1-[4-(substituted-phenyl)thiazol-2-yl]-3-(substituted phenyl)-1*H*-pyrazole-4-carbaldehyde **15**. The target compounds were synthesized starting from acetophenone **12** which were converted into thiosemicarbazones **13**. The thiosemicarbazones **13** were converted into thiazoles **14** *via* Hantzsch reaction with various phenacyl bromides. The thiazoles **14** were further treated with Vilsmeier-Haack reagent to furnish the target compounds **15**.



Scheme 4

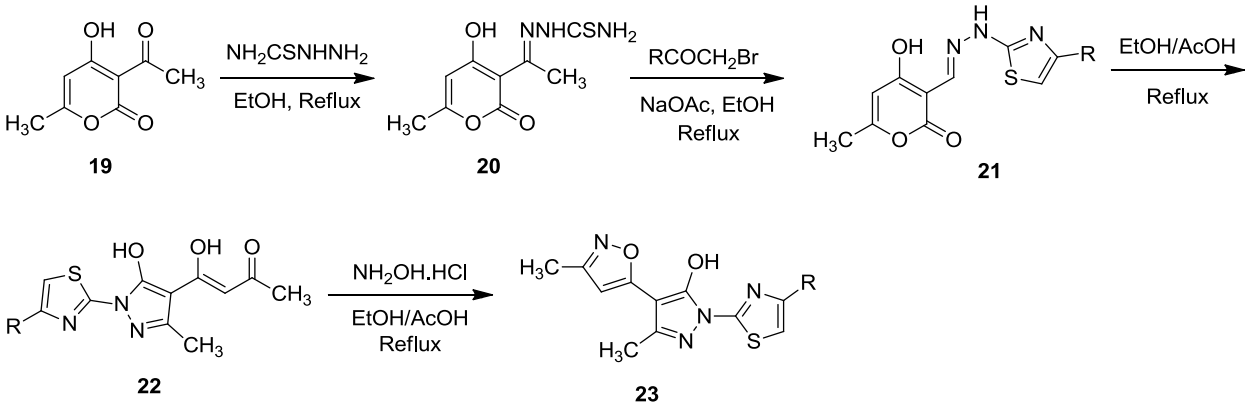
Mandawad et al (2013) reported the synthesis of 1-thiazolyl-2-pyrazolines **18** from 4,5-dihydropyrazole-1-carbothioamides **17** on treatment with p-chlorophenacyl bromide in polyethylene glycol. 4,5-Dihydropyrazole-1-carbothioamides **17** were synthesized from heterocyclic chalcones **16** on treatment with thiosemicarbazide using NaOH as a base.



Scheme 5

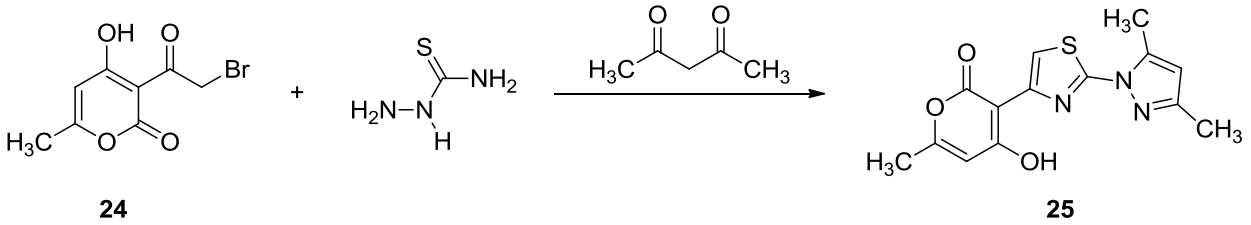
Mor et al (2012) reported the synthesis of 1-(4-(4-substituted-phenyl)thiazol-2-yl)-3-methyl-4-(3-methylisoxazol-5-yl)-1H-pyrazol-5-ols **23**. The thiosemicarbazone **20** was prepared in high yields upon treatment of 2-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one (dehydroacetic acid,

DHAA) with thiosemicarbazide in equimolar quantities which was smoothly converted into hydrazones **21** upon reaction with different 4-substituted phenacyl bromides in the presence of sodium acetate/ethanol. The hydrazones **21** thus obtained underwent rearrangement in ethanol-acetic acid mixture to afford the key intermediates i.e. 1-(5-hydroxy-3-methyl-1-substituted pyrazol-4-yl)-1,3-butadiones **22** which on subsequent treatment with hydroxylamine hydrochloride furnished the target compounds **23**.



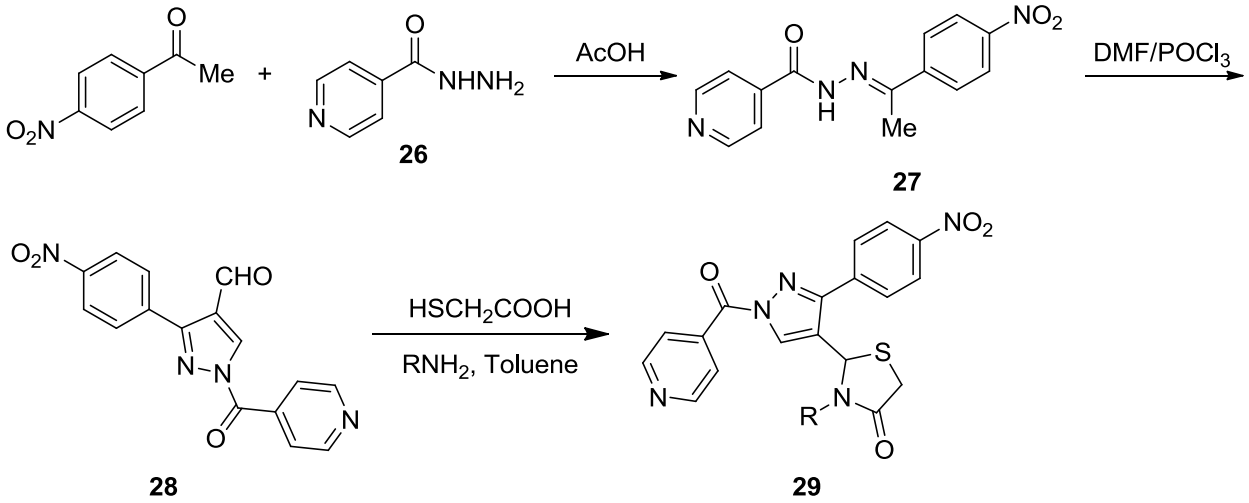
Scheme 6

Penta et al (2012) reported one pot synthesis of 3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)thiazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (**25**) *via* multicomponent approach in good yield.



Scheme 7

Visagaperumal et al (2009) reported the synthesis of pyrazolylthiazolidin-4-one **29** by the reaction of 1-isonicotinoyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbaldehyde (**28**) with 2-mercaptoacetic acid and several substituted aromatic amines in toluene. 1-Isonicotinoyl-3-(4-nitrophenyl)-1H-pyrazole-4-carbaldehyde (**28**) was prepared by using Vilsmeier-Haack reagent from (E)-N'-(1-(4-nitrophenyl)ethylidene)isonicotinohydrazide (**27**) which was synthesized from reaction of 4-nitroacetophenone and isonicotinohydrazide (**26**)**,** in the presence of acetic acid.



Scheme 8

5. Technical programme

i) Name of the experiment: Synthesis and spectral studies of 4-functional pyrazolylthiazoles and their biological investigation.

ii) Location of study: Chemistry Lab at Eternal University.

iii) Methodology:

a) Source of literature

Chemical abstracts, Indian Journal of Chemistry, Arkivoc, Indian Journal of Heterocyclic Chemistry, Asian Journal of Chemistry, Indian Journal of Pharmaceutical Sciences, Tetrahedron Letters, Tetrahedron, Journal of Indian Chemical Society, Iranian Journal of Pharmaceutical Research, Journal of Brazilian Chemical Society, and European Journal of Medicinal Chemistry etc.

b) Pre-laboratory work

The chemicals & reagents required for the synthesis of proposed compounds will be procured from reputed chemical suppliers like Merck, Ranbaxy, Qualigens, Himedia etc.

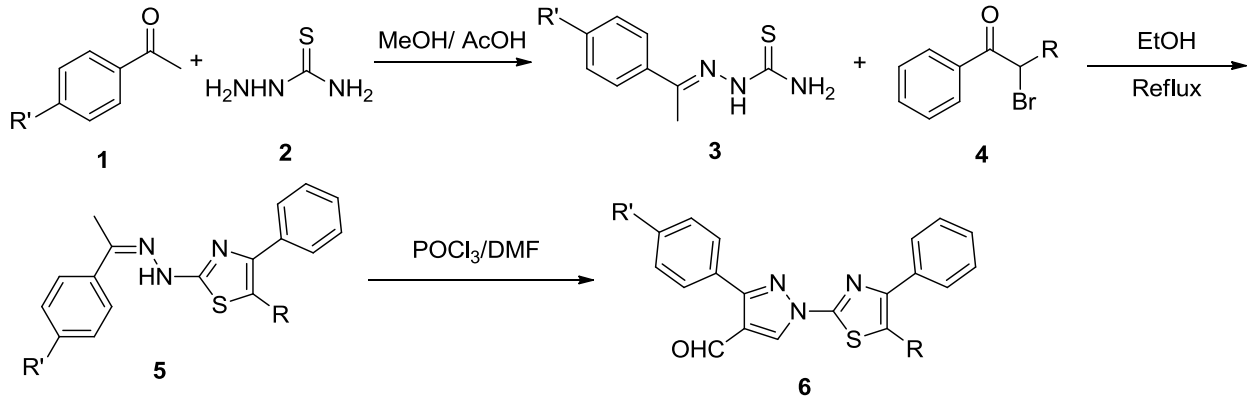
c) Laboratory work

Step 1: Synthesis

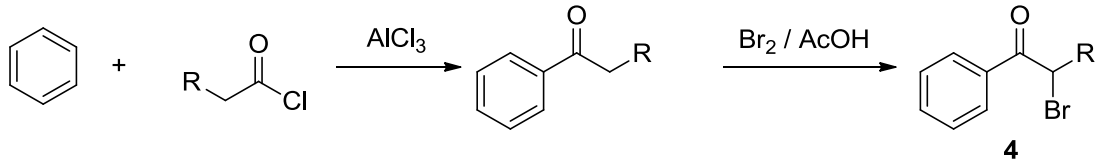
It will include standardising the reaction conditions for the synthesis of target compounds. Conventional methods of synthesis will be attempted. The completion of the reaction will be monitored by TLC. Advantages and feasibility of the methods will be analysed.

Plan of Work:

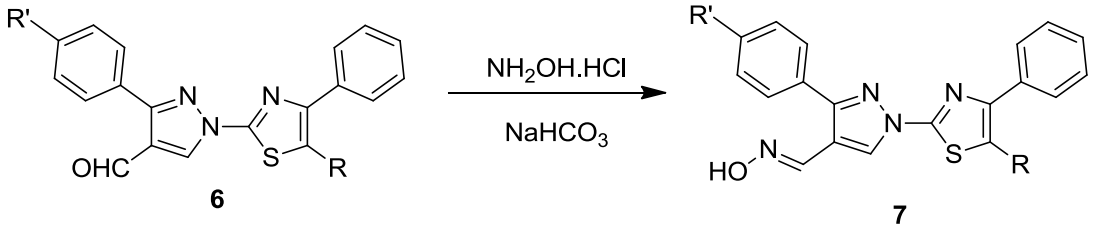
i. Synthesis of 4-formylpyrazolylthiazoles



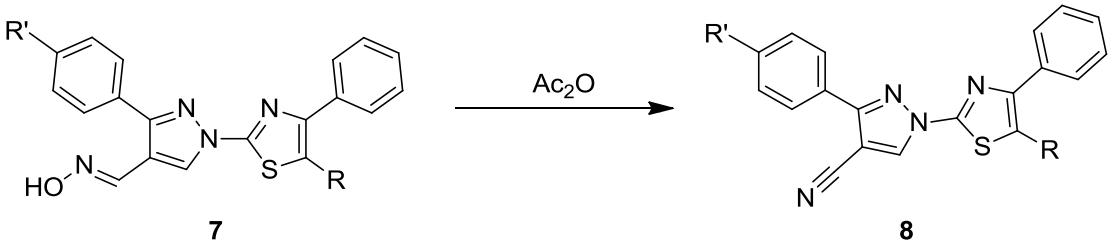
Preparation of Compounds **4:**



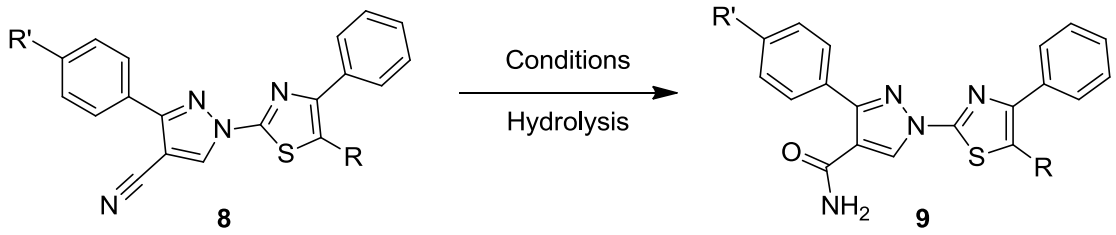
ii. Synthesis of 1H-pyrazole-4-carbaldehyde oximes



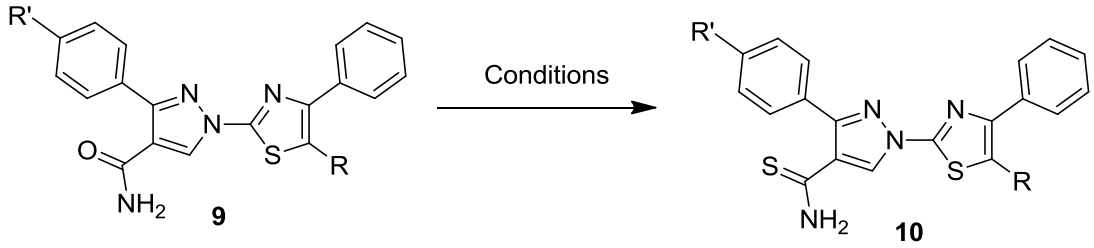
iii. Synthesis of 4-cyanopyrazoles



iv. Synthesis of 1H-pyrazole-4-carboxamides



v. Synthesis of 1H-pyrazole-4-carbothioamides



Step 2: Purification

The synthesized compounds will be purified by different methods like fractional distillation, recrystallization, and column chromatographic methods. The purity will be ascertained by TLC.

Step 3: Characterization

The synthesized compounds will be characterized by:

- Chemical tests for important functional groups.
- With various spectroscopic methods like IR, NMR, MS/LCMS etc.

iv) Observations to be recorded

- State of the compound (solid/liquid)
- If solid, colour of the compound
- Melting point if the compound is solid
- Yield of each compound
- Record and interpretation of IR, NMR, MS and other spectra as per requirements to characterize the desired compound.

5. Biological activity

The MIC values of different compounds will be determined against pathogenic Gram positive and gram negative bacterial and fungal species available in the microbiology Lab of Eternal University.

6. References

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